

Collective dynamics of molecular motors pulling on fluid membranes

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The collective dynamics of N weakly coupled processive molecular motors are considered theoretically. We show, using a discrete lattice model, that the velocity-force curves strongly depend on the effective dynamic interactions between motors and differ significantly from a simple mean field prediction. They become essentially independent of N if it is large enough. For strongly biased motors such as kinesin this occurs if $N \gtrsim 5$. The study of a two-state model shows that the existence of internal states can induce effective interactions.

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The collective behavior of molecular motors plays a crucial role in many biological phenomena ranging from intracellular and intra-flagellar transport to axonal transport [1, 2]. Molecular motors are often classified according to their processivity [3]. Processive motors rarely unbind from the track on which they are moving; they perform best when working in small groups and are therefore referred to as “porters”. Non-processive motors unbind from the track frequently, they work best in large groups and are referred to as “rowers”. Examples of “porters” are kinesin motors which move along microtubules, while classical myosin motors which move along actin filaments are examples of “rowers” [3].

The classification of motors into “porters” and “rowers” is based on their behavior when connected to a rigid or elastic cargo. The strong coupling between processive motors leads to an effective friction which results from motors which cannot move because other motors are bound to the track [3, 4]. A strong coupling between the motors indeed exists for a microtubule pushed by kinesin motors that are bound to a surface [2]. It is also important for describing myosin motors acting in skeletal muscles. The abundance of such systems has inspired several theoretical studies of the collective behavior of strongly coupled motors [5, 6].

In many cases, however, this description in terms of rowers and porters is not adequate since the coupling between the motors is negligible. An important class of systems where this happens is when motors, such as kinesin, move along microtubules and carry a load which is a lipid membrane, an ubiquitous situation in living cells. This occurs, for example, when kinesins or dyneins carry a vesicle along a microtubule [2]. Recent experiments have also shown that kinesin motors moving along a microtubule act collectively to pull membrane tubes from a vesicle [7].

In this Letter, we study theoretically the collective behavior of N processive motors pulling a tube out of a

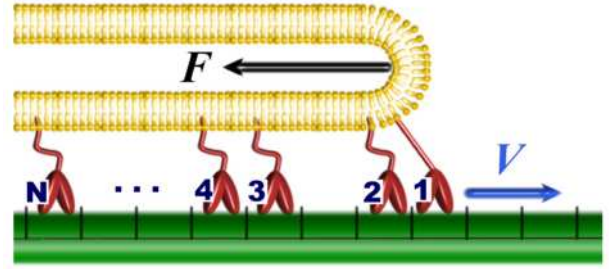


FIG. 1: Sketch of the system. N motors are pulling a membrane tube from a vesicle. The force F acts only on the leading motor (labeled 1). The remaining motors move in the absence of any applied force. At long time scales, all motors move at the same mean velocity V .

membrane and acting against the force needed to extract it [8], (Fig. 1). A fluid membrane can only exert a force on the motors at the leading edge of the tube where the normal to the surface has a component in the direction of motor motion. For simplicity we assume here that all the force is transmitted to the leading motor (Fig. 1). Our treatment is a reasonable approximation for kinesin motors carrying a vesicle subject to friction forces from the cytoskeleton. It could also be relevant for possible single molecule experiments where a bead is exerting a force on a single motor moving in front of several other motors.

We consider the collective behavior of the motors as a function of the applied force, F , the number of motors, N , and the effective interactions between the motors. An effective interaction is defined as the combined effect of the microscopic details of the system on the transition rates in a coarse-grained description (see discussion below). It is shown that the velocity-force curve $V_N(F)$ strongly depends on the interactions between motors and is different from that of a simple mean-field treatment in which independent motors share the force

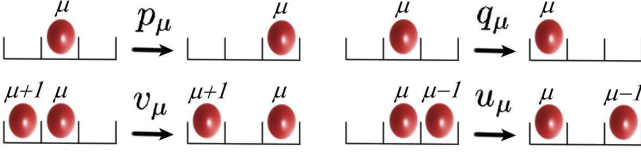


FIG. 2: Possible motor transitions and associated rates. The boxes and balls represent lattice sites and motors respectively.

$V_1(F/N)$. Moreover beyond a certain number of motors, the velocity-force curves are all indistinguishable for practical purposes. While the interactions do not play any role in the absence of external force, their effect becomes clearly visible as F increases. The possibility of extracting the nature of the effective interactions between motors from experiments is discussed. Finally we explore how the effective interactions in the coarse-grained description arise from a more microscopic two-state model.

In a coarse-grained description of the system we first model the motors as interacting biased random-walkers moving along a one-dimensional lattice. We assume that the motors are fully processive and never unbind from the filament (microtubule or actin) that acts as a track. The lattice constant ℓ is the periodicity of the filament. Each site can only be occupied by one motor which can move to a neighboring site if empty. We label the motors with an index $\mu = 1 \dots N$, with 1 labeling the motor on which the force is exerted (Fig. 1). The dynamics of the motors is specified by the hopping rates defined in Fig. 2 where the boxes represent sites on the lattice and a ball with index μ indicates that the site is occupied by motor μ .

The model is a generalization of the disordered exclusion model introduced in [9] which includes modifications of the rates due to nearest-neighbor interactions between the motors. The hopping rates are chosen as follows: $p_\mu = p$, $v_\mu = v$, $q_\mu = q$ and $u_\mu = u$ for $\mu \geq 2$; the rates of the leading motor ($\mu = 1$) depend on the external force [10]. Using Kramers rate theory [11], we assume for simplicity an Arrhenius dependence on the force so that $p_1 = pe^{-f\delta}$, $q_1 = qe^{f(1-\delta)}$ and $v_1 = ve^{-f\delta}$, where f is the force in units of $k_B T/\ell$ (k_B being the Boltzmann constant and T the temperature). The dimensionless parameter $0 < \delta < 1$ characterizes the position of the energy barrier between the two neighboring lattice sites. Attractive effective interactions correspond to reduced hopping rates ($v < p$, $u < q$) and repulsive effective interactions to increased hopping rates ($v > p$, $u > q$). We refer to the case $v = p$ and $u = q$ as neutral.

It is instructive to first consider a system with only two motors. This case may be solved exactly in the long-time limit. For any finite force the probability of finding the motors k sites apart decays as $[(p_1 + q)/(p + q_1)]^k$. The average number of sites between the two motors is therefore finite and decreases with the force. Since the

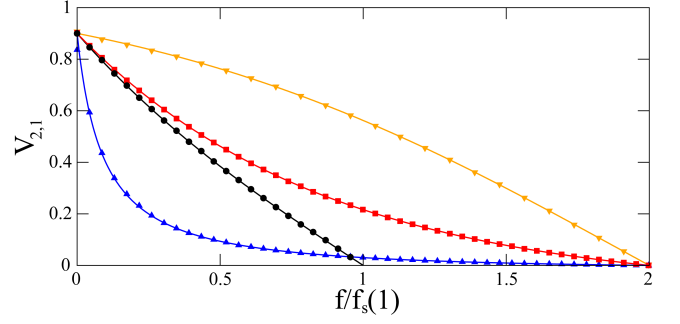


FIG. 3: Velocity-force curves of 2 motors in the limits of attractive, repulsive and neutral interactions. Analytical solutions of Eq. (1) (solid lines) and Monte Carlo simulations (symbols). For all cases $p = 1.0$, $q = 0.1$ and $\delta = 0.5$. The rates v and u are: $v = 0.1, 1.0, 10.0$ and $u = 0.01, 0.1, 1.0$ for attractive (triangle up), neutral (square) and repulsive (triangle down) interactions respectively. The velocity-force curve for a single motor is also plotted for comparison (circle). The ratio $v/u = p/q$ so that $f_s(2) = 2f_s(1)$. All rates are in units of p .

motors cannot overtake each other, their velocities are equal and read:

$$V_2 = \frac{v_1(p - q) + u(p_1 - q_1)}{(v_1 + u) + (p - q) - (p_1 - q_1)}. \quad (1)$$

For comparison, the velocity of a single motor within this model is $V_1 = p_1 - q_1$. The maximum force that the motors can exert (stall force) is the force for which the velocity vanishes. The stall force of a single motor is given by $f_s(1) = \ln(p/q)$, while using Eq. (1) the stall force of two motors is

$$f_s(2) = \ln\left(\frac{pv}{qu} + \frac{p}{q} - \frac{v}{u}\right). \quad (2)$$

The stall force is not necessarily twice the stall force of a single motor. It is a function of the rates ratio v/u , which depends on the interactions between the motors, and can be either larger or smaller than $2f_s(1)$ depending on whether $v/u > p/q$ or $v/u < p/q$ respectively.

The velocity V_2 is plotted for various values of v and u in Fig. 3 where, for clarity, we set $v/u = p/q$. The velocity V_1 of a single motor is also shown in the figure. The general shape of the velocity-force curve is highly sensitive to the interactions. For strong enough attractive interactions the velocity of two motors is smaller than that of a single motor up to a certain value of the force. At an interaction dependent point the two curves cross and the two motors become faster than a single motor for large enough forces. An experimental signature of this type is a clear demonstration of attractive interactions between the motors.

We now turn to the general case with N motors. Using the result of [9], an exact expression of the velocity can

be obtained in the neutral case where $v = p$ and $u = q$ on a ring geometry. In the limit where the number of vacancies in front of the first motor ($\mu = 1$) is infinite, the periodic boundary conditions do not influence the results. Building on the results of Ref. [9] one finds

$$V_N = p \frac{[1 - e^f(q/p)^N][1 - q/p]}{e^{f\delta}[1 - q/p] + e^f[q/p - (q/p)^N]}. \quad (3)$$

In the neutral case, for any number of motors $f_s(N) = Nf_s(1)$. For large N , the slope and therefore the velocity near stall force, decrease exponentially with the number of motors as $(q/p)^N$. Even in the neutral case, the velocity-force curve is different from the naive mean-field prediction $V_N(F) = V_1(F/N)$. In the absence of force, the velocity is independent of the number of motors. The slope of the velocity-force curve for vanishing forces is negative and converges exponentially fast with N to $-(1 - q/p)[q + (p - q)\delta]$. The larger the number of motors the smaller the absolute value of the slope. In particular, these results imply that for any $N \gg -1/\ln(q/p)$ the velocity force curves are indistinguishable for any practical purpose.

Close to stall force, the velocity and the stall force can be obtained in the presence of interactions in the limit where $p \gg q$, $p \gg u$ and $v \gg u$: the motors then form a compact cluster and the movement in either direction occurs by propagation of a vacancy from one end to the other. This argument leads to

$$V_N = v_1 v / q_1 - u(u/p)(u/v)^{N-3}. \quad (4)$$

One can check that this is in agreement with the general result for two motors and with the result for N motors in the neutral case. The normalized stall force for N motors in this limit is then

$$\begin{aligned} f_s(N)/(Nf_s(1)) &= \ln(v/u)/\ln(p/q) \\ &- (\ln(v/u)/\ln(p/q) - 1)/N \end{aligned} \quad (5)$$

As for two motors, the stall force only depends on the rate ratios v/u and p/q . If $v/u > p/q$ the normalized stall force per motor increases with the number of motors and saturates at a value larger than 1 for many motors. It has the opposite behavior when $v/u < p/q$.

We have also performed continuous time Monte Carlo simulations (see e.g. [12]) to test the effect of interactions between motors. Similarly to the case of two motors, when $v/u \neq p/q$ the stall force is only a function of the ratio v/u (Fig. 4a). When $v/u = p/q$ the stall force always satisfies $f_s(N) = Nf_s(1)$ as expected. This statement can be made rigorous by showing that with $v/u = p/q$ at the stall force detailed balance holds [13]. The general shape of the velocity-force curve reveals that as in the case of two motors, when the interactions are strongly attractive, there is a cross-over from a low force regime where the velocity is lower than that of a single

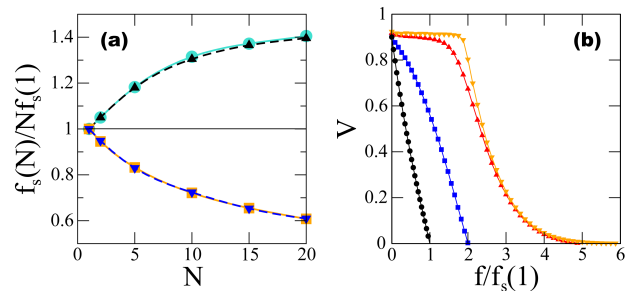


FIG. 4: (a) Stall force as a function of N for various types of interactions. Both for attractive ($v = 0.7$, $u = 0.5$; circles) and repulsive ($v = 1.54$, $q = 1.1$; triangles up) interactions, the value of the stall force, $f_s(N)$, is the same and larger than $Nf_s(1)$ as $v/u = 1.4 > p/q$. When $v/u = 1.1 < p/q$, $f_s(N) < Nf_s(1)$ and it has also the same value for both attractive ($v = 0.55$, $u = 0.5$; squares) and repulsive ($v = 1.21$, $u = 1.1$; triangles down) interactions. (b) Velocity-force curves in the case of repulsive interactions between highly biased motors ($p = 1$, $q = 0.1$, $v = 10$, $u = 1$ for 1 (circles), 2 (squares), 5 (triangles up), 10 (triangles down) motors; $\delta = 0.5$. All rates are in units of p .

motor to a regime where it is higher. An important result of the simulations is that, similarly to the neutral case, for any given type of interaction the velocity-force curves are all nearly identical above a certain number of motors. We stress that the comparison between the velocities of many and one motor could serve as an experimental test to sort out attractive or repulsive interactions. In the presence of repulsive interactions, the velocity V_N of N motors is always larger than the velocity of 1 motor and the velocity force curves all collapse on a single curve if $N \gtrsim 7$, ($p/q = 10$) (Fig. 4b). In the presence of strong enough attractive interactions the velocity is always smaller than that of a single motor for small forces but becomes larger at larger forces. The velocity-force curves collapse if $N \gtrsim 5$, ($p/q = 10$). Experimentally one should expect a velocity-force curve independent of the number of motors if a few motors act collectively. The observed stall force could also be much smaller the predicted theoretical one since for many motors, the velocity reaches negligible values way below stall force.

In the above discussion the nature of the effective interaction (neutral, attractive or repulsive) between the motors was assumed. We now argue that for motors with several internal states, one expects generically non-neutral interactions on long times and large length-scales. We use the example of a two-state model [14] (Fig. 5a, inset). In the strongly bound state (1) the motor feels the sawtooth potential, $W_1(x)$, with a period ℓ , an amplitude $5k_B T$ and a short segment of the sawtooth of length $a = 0.2\ell$. In the weakly bound state (2) the potential $W_2(x)$ is constant. The motors change from state 1 to state 2 and vice-versa with local excitation rates $\omega_1(x)$ and $\omega_2(x)$ respectively. The transition rates, in arbitrary

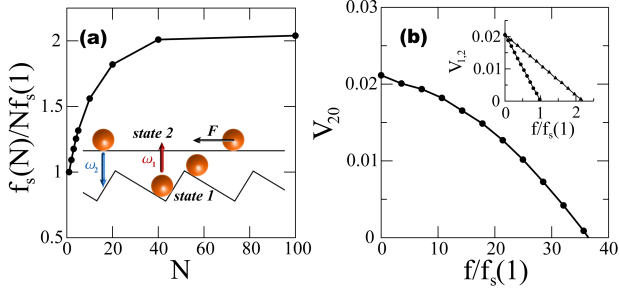


FIG. 5: Simulation results for motors with two internal states (two-state model) and only excluded volume interactions. (a) Stall force as a function of the number of motors. The value of the stall force is larger than $Nf_s(1)$. (b) Velocity-force curve for 20 motors. The inset in (a) sketches the two-state model, and the one in (b) shows the velocity-force relation for 1 (circles) and 2 (triangles up) motors.

units, are given by $\omega_1(x) = \frac{\Omega}{\alpha\sqrt{\pi}} \exp[-(x \bmod \ell)^2/\alpha^2]$ with $\Omega = 2$, $\alpha = 0.05\ell \ll a \ll \ell$ and $\omega_2(x) = 0.2$. We assume only hard core interactions between the motors. These are captured by a repulsive potential $U(y)$ which depends on the distance, y , between the motors. The potential chosen is the shifted repulsive part of a Lennard-Jones potential vanishing at $y > 2^{1/6}\sigma = 1.68\ell$, with an amplitude $\varepsilon = 0.05k_B T$. The interaction range is $\sigma = 1.5\ell$. We have verified that our results remain qualitatively the same upon changing the details of the potential and the values of the parameters.

We numerically simulate the model using Langevin dynamics for the motors. The equations for motor μ in state s_μ read

$$\xi \frac{dx_\mu}{dt} = -\frac{dW_{s_\mu}(x_\mu)}{dx} - \frac{d}{dx_\mu} \sum_{\kappa \neq \mu} U(x_\mu - x_\kappa) + F\delta_{\mu,1} + \eta, \quad (6)$$

where F is the external opposing force, and $\xi = 50$ is the dimensionless friction coefficient of the motor. The random force is described by the noise term $\eta = r\xi\sqrt{\frac{6k_B T}{\xi dt}}$, where r is a random number taken from a uniform distribution from -1 to 1. These equations are coupled to standard Monte Carlo steps for the transitions between the bound states 1 and 2. Initially, the N motors are placed randomly at distances exceeding $2^{1/6}\sigma$, so that the interaction energy $U(y)$ vanishes. Throughout the simulation, we follow the position of the first motor and determine its velocity at long times.

The velocity-force curve obtained from the simulations for 20 motors is plotted in Fig. 5b. Since the parameters were chosen so that the stall force of one motor is small, the velocity-force relation is nearly linear for a small number of motors (Fig. 5b, inset). Increasing the number of motors reveals the non-linearities. The comparison between the general shape of the curve for 20 motors (Fig. 5b) with the ones obtained from the coarse-

grained model, suggests that the existence of two internal states for the motors leads to effective repulsive interactions. The stall force is plotted in Fig. 5a as a function of the number of motors. For a given N , it is larger than $Nf_s(1)$, indicating that the effective rates for forward and backward movement in the equivalent coarse-grained model are such that $v/u > p/q$. As the number of motors is increased this effect becomes more important and saturates for large N . Overall, these results are consistent with those obtained for weakly biased random-walkers with repulsive interactions.

We now give a qualitative discussion of the two-state model for two motors. A simple mean-field approach would assume that the effect of the second motor is to contribute with a mean force, which is that produced by the single motor at the actual velocity of the two motors. This yields $V_2(F) = V_1(F/2)$. In this approximation, the two motors equally share the force. This result holds only for sufficiently smooth long range interaction potentials.

Going beyond mean field, we have identified two configurations that contribute most to the increase of both the stall force and the velocity. If the leading motor carrying the force is in the unbound state and the trailing motor in the bound state, the force exerted by the filament potential on the trailing motor pushes the leading motor forward. This is best seen in the case where the diffusion constant of the motors is very small and $f > 0$: the velocity of a single motor is small, as is evident from the ratchet potentials, but the velocity of the two motors remains finite as the trailing motor pushes the leading motor over the potential barrier. This effect is very sensitive to the mismatch between σ and ℓ . On the other hand, if the two motors are in the unbound state the entropic repulsion between the two motors biases forward the motion of the leading motor. Using these ideas one can explicitly check in the limit where σ is close to a multiple of ℓ , that $f_s(2) > 2f_s(1)$, the difference increasing with the diffusion coefficient of the motors [13].

In conclusion, we have shown using various models of molecular motors that the collective behavior of a cluster of weakly coupled motors depends on their dynamic interactions and is very different from both the mean field prediction and from the behavior of strongly coupled motors.

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